

Chapter 16

MILITARY PERSONNEL WITH POSTDEPLOYMENT DYSPNEA: CHRONIC LUNG DISEASE AND THE ROLE OF SURGICAL LUNG BIOPSY

MICHAEL J. MORRIS, MD^{*}; AND DANIEL E. BANKS, MD[†]

INTRODUCTION

LUNG DISEASE AND DEPLOYED MILITARY PERSONNEL

CONSTRICTIVE BRONCHIOLITIS

Radiographic Findings

Pathological Findings of Constrictive Bronchiolitis

Clinical Syndromes of Constrictive Bronchiolitis

Deployed Military Personnel and Constrictive Bronchiolitis

Indications for Surgical Lung Biopsy

EVALUATION OF WORLD TRADE CENTER RESPONDERS

SUMMARY

^{*}Colonel (Retired), Medical Corps, US Army; Department of Defense Chair, Staff Physician, Pulmonary/Critical Care Medicine and Assistant Program Director, Internal Medicine Residency, San Antonio Military Medical Center, 3551 Roger Brooke Drive, Fort Sam Houston, Texas 78234

[†]Lieutenant Colonel, Medical Corps, US Army; Professor, Department of Medicine, Uniformed Services University for the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814; Director and Editor in Chief, Borden Institute, 2478 Stanley Road, Fort Sam Houston, Texas 78234; Staff Physician, Department of Medicine, Brooke Army Medical Center, 3551 Roger Brooke Drive, Fort Sam Houston, Texas 78234

INTRODUCTION

Deployment of military personnel to Iraq and Afghanistan in support of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom has resulted in unique medical challenges due to the sustained length of combat operations with multiple deployments and the hostile desert environment. Although traumatic brain injury, posttraumatic stress disorder, and traumatic amputations have come to the forefront of military medical efforts, other medical challenges remain. Environmental sampling by the US Army Public Health Command (Aberdeen Proving Ground, MD) has established that ambient particulate matter (PM) levels from this region are elevated mainly from sandstorms and geological dusts. However, other factors (eg, fumes from burn pits, urban air pollution, and vehicle exhaust)—as well as the increased rate of cigarette smoking—remain respiratory hazards to deployed personnel.¹

The joint US Department of Veterans Affairs (VA) and the US Department of Defense (DoD) Airborne Hazards Symposium held in 2012 in Arlington, VA, specifically addressed the potential relationship between airborne hazards and lung disease in deployed military personnel. This conference was organized as a response to numerous concerns raised in publications such as the 2011 report by the Institute of Medicine, *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan*, that states, “Service in Iraq or Afghanistan might be associated with long-term

health effects, particularly in highly exposed and/or susceptible populations, mainly because of high concentrations of particulate matter.”² The report determined that there is “limited/suggestive evidence of an association between exposure to combustion products and reduced pulmonary function in these populations.”² Two primary issues were at the forefront of the discussion during the conference:

1. Is there an identifiable link between deployment and the development of lung disease in general and, in particular, chronic lung diseases such as constrictive bronchiolitis (CB) as described by King et al³?
2. What type of clinical evaluation should be performed on military personnel returning from deployment with respiratory symptoms, but whose pulmonary function testing (PFT) results are normal and radiographic findings are unremarkable?

This chapter addresses the diagnosis of CB and other lung diseases associated with deployment to southwest Asia (SWA) as currently described in the medical literature. Furthermore, it focuses on the published recommendations concerning the evaluation of radiographic findings in symptomatic patients and the current indications for surgical lung biopsy.

LUNG DISEASE AND DEPLOYED MILITARY PERSONNEL

There is a minimal amount of published data associating deployment to SWA with chronic lung disease. Specifically, there is a lack of both cross-sectional and longitudinal studies on diagnosed lung disease. Although the survey data of deployed personnel during Operation Desert Storm (often referred to as the First Gulf War) and OIF/Operation Enduring Freedom demonstrated an increase in reported respiratory symptoms, no longitudinal data have documented an associated increase in chronic lung disease.⁴ Likewise, additional epidemiological studies have not shown an increase in defined chronic lung disease from these conflicts.⁵ A well-described cluster of deployment-related acute eosinophilic pneumonia cases in military personnel were initially reported during the early years of OIF. Eighteen cases of acute eosinophilic pneumonia were diagnosed among 183,000 military personnel deployed in or near Iraq in 2004.⁶ Continued data collection from Landstuhl Regional Medical Center in Germany now shows 44 diagnosed cases, with an average bronchoalveolar lavage (BAL) eosinophilia of $36.8\% \pm 20.9\%$. Ninety-three percent of the patients were smokers, and 65% required mechanical ventilation.⁷

The primary respiratory concern for military personnel in general is asthma. However, very limited data exist on the effects of deployment on asthma. A survey of Army personnel deployed to SWA identified 5% with a previous diagnosis of asthma.⁸ In this group, both asthmatics and nonasthmatics reported a similar increase in respiratory symptoms during deployment. A retrospective review of VA medical records based on diagnostic codes with limited PFT data noted higher rates of asthma (6.6% vs 4.3%, $p < 0.05$) in deployed military compared with nondeployed personnel.⁹ A more in-depth DoD review of asthmatics undergoing a formal medical “fitness-for-duty” evaluation could not establish a definitive relationship between deployment and the diagnosis of asthma. DoD investigators reviewed 400 patient records, and the diagnosis of asthma had been objectively confirmed in 78% of the patients either by spirometry or bronchoprovocation testing. Only 25% of asthmatic individuals were diagnosed postdeployment, and no differences in spirometry or asthma severity were noted based on deployment history.¹⁰

Preliminary data on interstitial lung disease (ILD) diagnoses collected by military researchers showed a low overall number of cases (1.5% of military patients evaluated in Army pulmonary clinics) and were primarily attributable to sarcoidosis (53%). Fifty percent of sarcoidosis cases occurred in never-deployed personnel,

and no differences in disease stage or severity were noted when comparing a pre- and postdeployment diagnosis of sarcoidosis.¹¹ Further collection of data to identify the prevalence of pulmonary disease in military personnel and veterans is under way in a variety of studies being conducted by DoD researchers.

CONSTRUCTIVE BRONCHIOLITIS

CB, also referred to as “bronchiolitis obliterans,” has been associated with numerous identified causes and is recognized to occur in various clinical settings. Clinically, it may be attributable to transplantation, medical causes, and inhalation injury. Foremost, CB is well recognized as a common complication of lung transplantation (occurring in up to 60% of patients) and is less frequently associated with bone marrow or stem cell transplantation (approximately 10%). Other noninhalational causes include postinfectious inflammatory responses (*Mycoplasma pneumoniae*, adenovirus, and influenza), drug reactions (gold, penicillamine), connective tissue disorders (rheumatoid arthritis and scleroderma), and other miscellaneous disorders (ulcerative colitis, Stevens-Johnson syndrome, neuroendocrine cell hyperplasia, and paraneoplastic pemphigus).¹²

The disorder may also be idiopathic and has been only occasionally reported as cryptogenic “adult” bronchiolitis. An initial case series from 1993 first described four nonsmoking females with chronic cough and dyspnea without any features clinically consistent with known pulmonary diseases. Three of these patients had increased bronchovascular markings on the chest X-ray radiograph (CXR). A reduced diffusing capacity and obstructive defects were identified in three patients. All were diagnosed with CB by open lung biopsy.¹³ Further descriptions of cryptogenic CB have noted typical imaging features of mild hyperinflation on CXR. PFT may demonstrate obstruction, increased lung volumes, airflow limitation, lack of response to bronchodilators, and reduction in diffusing capacity of the lung for carbon monoxide (DLCO).¹⁴

CB may also be the result of inhalation injury and has been described in association with a variety of toxic fumes, irritant gas, mineral dust, organic dust, or volatile flavoring agent exposures.¹⁵ Toxic fume exposures that typically cause CB include sulfur dioxide, ammonia, chlorine, methylisocyanate, or fire smoke. Inhalation of nitrogen dioxide (as in Silo-Fillers’ disease) or sulfur dioxide is the classic example of a three-stage illness following toxic fume exposure. Immediately postexposure, there may be burning of the mucous membranes (eyes and throat) with minimal respiratory symptoms noted. An asymptomatic latent period of a few hours may be followed by the development of acute respiratory distress syndrome. If the patient survives, there will be a second latent period followed by the development of bron-

chiolitis obliterans with obstructive pneumonia (in the case of nitrogen dioxide) or CB (after sulfur dioxide exposure).¹³ Other detailed reports have implicated diacetyl exposure from butter flavoring in microwave popcorn workers,^{15,16} mustard gas exposure during the Iran-Iraq war,^{17–19} and dust from the World Trade Center (WTC) collapse²⁰ as causes of CB. In East Asian countries, oral toxin-related CB has been linked to consumption of the leafy vegetable *Sauropus androgynous* used for weight control.^{21,22}

Radiographic Findings

As described in multiple studies, the routine CXR is generally of minimal value in CB because often, chest imaging may either be normal or show a mild degree of hyperinflation. Typical high-resolution computed tomography (HRCT) findings in patients with CB show increased bronchiolar wall thickening and expiratory air trapping. This is recognized as the classic “mosaic pattern,” an alternating pattern of increased and decreased density of the pulmonary lobules. The most striking HRCT feature is the finding of lobular or segmental areas of decreased lung attenuation, interpreted as air trapping with oligemia associated with narrowing of pulmonary vessels.²³ Bronchiectasis and bronchiolectasis are late findings in more severe disease. A composite computed tomography (CT) score may be useful for early detection in lung transplant patients. This score correlates with a decreasing forced expiratory volume at 1 second (FEV₁) and includes bronchiectasis, mucus plugging, airway wall thickening, consolidation, mosaic pattern during inspiration, and air trapping during expiration.²⁴

The use of HRCT to detect CB has been studied extensively because it may provide earlier detection of disease. Breatnach and Kerr²⁵ first described the CXR findings in 13 known CB patients. The researchers reported what would become recognized as the characteristic CXR appearance of diminished midzone to lower zone vasculature and mild hyperinflation in seven patients. Padley et al²⁶ characterized the appearances of 18 patients with CB on HRCT (biopsy confirmed in six) and correlated these findings to PFT results. Sixteen of 18 performed PFTs with a mean FEV₁ of 41% predicted, a mean residual volume (RV) of 165% predicted, and an average FEV₁/forced vital capacity (FVC) of 61.6%

predicted. There was no significant correlation between the extent of HRCT abnormalities and the static lung volumes or impairment in gas diffusion. The most common abnormalities were patchy areas of decreased parenchymal attenuation ($n = 15$), subsegmental ($n = 12$) and segmental ($n = 6$) bronchial dilatation, and centrilobular branching structures ($n = 5$).

Studies by Leung et al²⁷ and Worthy et al²⁸ showed that air trapping on expiratory scans was both sensitive (80%–91%) and specific (80%–94%) in diagnosing bronchiolitis obliterans in lung transplant recipients. The role of HRCT in the early diagnosis of CB is less clear. Lee et al²⁹ correlated thin-section CT findings with biopsy results in 28 patients following lung transplant, 7 of whom had pathological features of CB. Using an air trapping score >3 (based on a maximum score of 4 for $>75\%$ involvement), the sensitivity of expiratory CT was 74%, specificity was 67%, and accuracy was 71%.

Pathological Findings of Constrictive Bronchiolitis

A detailed discussion of the pathological features of CB is provided in Chapter 15 (The Problems With Constrictive Bronchiolitis: Histopathological and Radiological Perspectives). In brief, the pathological features of CB include the following:

- peribronchiolar fibrotic process that surrounds, rather than fills, the lumen;
- submucosal collagenous fibrosis with progressive concentric narrowing associated with luminal distortion;
- fibrosing bronchiolitis that preferentially involves membranous bronchioles and is characterized by fibrosis of the stroma (the muscle layer may be hypertrophic in early lesions, atrophic in late stages, and replaced by fibrotic tissue at the end stage); and
- concentric narrowing or obliteration of the airway lumen due to submucosal lesions occurring in the membranous bronchioles and sparing the distal respiratory bronchioles.

Clinical Syndromes of Constrictive Bronchiolitis

The largest case series (29 patients) of nontransplant and noninhalational CB was published in 2008.³⁰ The mean age was 54 years, and 69% of the patients were females. All presented primarily with dyspnea and/or cough, and only 14% reported a smoking history. Identified causes in 20 patients (69%) included

- rheumatoid arthritis,
- hypersensitivity pneumonitis,
- multiple carcinoid tumorlets,
- Sjögren's syndrome,
- paraneoplastic pemphigus,
- inflammatory bowel disease, and
- Swyer–James syndrome.

An underlying cause was not identified in nine patients (31%) and was considered to be cryptogenic CB. CXRs were normal in 28% of the patients. Hyperinflation was the primary abnormality seen in an additional 55% of patients. HRCT showed mosaic perfusion and air trapping in all patients, whereas bronchiectasis was noted in an additional 21 patients. PFTs were abnormal in all patients, and 86% of patients had an obstructive defect (exceptions were those patients with hypersensitivity pneumonitis and extreme obesity). Mean PFT values included

- FEV_1 (% predicted) = 42 ± 16 ,
- FVC (% predicted) = 60 ± 14 ,
- $FEV_1/FVC = 0.55 \pm 0.15$,
- total lung capacity (% predicted) = 104 ± 19 ,
- RV (% predicted) = 176 ± 65 , and
- DLCO (% predicted) = 79 ± 21 .

Another series presented 19 biopsy-proven CB patients with varying clinical presentations.³¹ Of those, 11 demonstrated airflow limitation, 1 had a restrictive pattern, 1 had a mixed pattern, 2 had isolated gas trapping, and 4 had normal spirometry. Mild-to-moderate bronchiolar inflammation in the subepithelial layers, the adventitial layer, or both, was invariably present in all patients. HRCT performed in 10 patients revealed inspiratory (50%) and expiratory air trapping (100%), ground-glass opacities (70%), bronchial wall thickening (50%), bronchiectasis (20%), and centrilobular nodules (20%). Interestingly, six patients had a prior clinical diagnosis of asthma with progressive deterioration of lung function prior to the diagnosis of CB. One patient died, 4 patients eventually underwent lung transplantation, and 6 additional patients responded to antiinflammatory therapy. Follow-up clinical evaluations were not available in the remaining patients.

In popcorn workers with diacetyl exposure, nine patients were described in detail by Akpinar-Elci et al.¹⁶ after the initial report was published in 2002. All workers had respiratory complaints of cough, dyspnea, wheezing, myalgia, and fatigue. Eight of the nine patients underwent HRCT. All showed marked bronchial wall thickening and mosaic attenuation with air trapping on expiratory imaging. Mild cylindrical bronchiectasis was seen in five cases, and mild upper lobe volume loss and subpleural nodularity suggestive of fibrosis were seen in three cases. Initial spirometry noted impairment with FEV_1 ranging from 14.0% to 66.8%

predicted, FVC of 24% to 84% predicted, and FEV_1/FVC of 23% to 75%. Thoracoscopic lung biopsy was performed and was consistent with CB in two of three cases. After leaving employment, there was stabilization of lung function among the patients, although five patients were on lung transplantation waiting lists. An additional report describing the screening of 175 workers employed in a diacetyl production plant located in The Netherlands showed three cases consistent with CB among the process operators with highest exposure.³² All cases had moderate-to-severe airways obstruction with hyperinflation with air trapping on HRCT. A video-assisted thoracoscopic lung biopsy was performed in one case. Some histological sections showed emphysema and chronic bronchiolitis, reflecting nonspecific small airway disease but no sign of CB.

Studies of Iranian soldiers exposed to mustard gas in the 1980 to 1988 Iran-Iraq war reported ILDs (including CB) in patients with chronic respiratory complaints.^{18–20} Of 15 patients who underwent surgical lung biopsy, 6 had severe and 9 had mild exposure to mustard gas 20 years earlier. Thirteen patients had normal spirometry, 1 had obstruction, and 1 had mild restriction. Six patients in the mild exposure group and 3 in the severe exposure group showed evidence of >25% air trapping on chest HRCT. Pathological findings varied; 33% of the patients (both mild and severe exposure) had definitive findings of CB and various other types of bronchiolar injury.

Each of these case series provides insight on the unique and clinically distinct spectrum of disease associated with the diagnosis of CB. Etiologies for CB range from various inflammatory diseases to inhalational causes, as seen in diacetyl and mustard gas exposures. In many cases, the etiology remains undetermined.

Deployed Military Personnel and Constrictive Bronchiolitis

In 2011, King et al³ reported the outcomes of evaluations addressing the respiratory symptoms of 80 military personnel who had returned from Iraq and Afghanistan with dyspnea on exertion. Patients comprising this case series had varied deployment exposures. Self-reported inhalational exposures included the 2003 Mishraq Sulfur Mine fire, dust storms, burn pits, combat smoke, and human waste. Forty-nine of the patients underwent surgical lung biopsy. No members of the nonbiopsied group (0/31) and 36/49 (73%) in the biopsied group reported exposure to the 2003 Mishraq Sulfur Mine fire. A pathological diagnosis of CB was made in 38 (78%) of the biopsied patients. Evaluation consisted of complete lung function testing (results of postbronchodilator testing were not reported) and HRCT in this group, whereas cardiopulmonary exercise testing was completed in 30/38 (79%) soldiers diagnosed with CB. The methacholine

challenge test was performed in 12/38 (32%) patients. Additional diagnostic testing, such as flexible laryngoscopy or bronchoscopy, was not reported. Spirometry was normal in the majority of patients diagnosed with CB because 16% had evidence of obstruction or restriction. Full PFTs revealed that half of the patients had a reduction in DLCO (mean value of 73.4 ± 15.4), but the reported mean total lung capacity (96.1 ± 15.5) did not reflect hyperinflation; mean RV values were not reported. Chest radiography was normal in 37/38 patients. HRCT showed mild air trapping in 16%, but the diffuse radiographic pattern of mosaicism was not described in any patients. The pathological diagnoses of the lung biopsy specimens were made by two clinical pathologists. The authors associated these findings with inhalational exposures during deployment.

An epidemiological study conducted by the US Army Public Health Command found no increase in the number of postdeployment medical encounters among military personnel exposed to the 2003 Mishraq Sulfur Mine fire, compared with unexposed personnel: “This exploratory analysis did not show a definite link between sulfur fire exposure in Iraq and either chronic or recurring respiratory diseases.”³³ The report did not address any specific reported illness, but only reported whether there were an excess number of respiratory complaints related to acute exposures. An important issue not addressed was the long-term outcome of these soldiers. According to the previously cited report, the majority of soldiers had symptoms with high levels of exercise only. No outcome data was provided that would identify whether these soldiers had a progressive clinical course. Follow-up questionnaire information is only available for 43% of them. It is important to know the severity and chronicity of their illness as a baseline, and to undertake further longitudinal evaluation to determine if there was a progressive worsening of symptoms, a decline in exercise tolerance or lung physiological indices, or a response to specific therapies.

Does the pathological finding of CB on the surgical lung biopsy equate with the clinical syndrome of CB or bronchiolitis obliterans in these patients? We summarized the clinical, physiological, and radiological data from manuscripts describing patients with non-transplant-related CB and contrasted this information with the findings in the King et al³ article (Table 16-1).³⁴ Manuscripts that addressed the clinical features and outcomes of CB in transplant patients were excluded because confounding issues (eg, graft-versus-host response or infections in the immunosuppressed host) occur with frequency and mask the features of CB. At 23.5%, smoking was less prevalent in the historical CB population as compared with the rate of 34.2% in the soldiers. PFT data show that the presence of nonreversible obstruction (89.2%) is consistent with a diagnosis of CB, yet the patients from King et al³ were rarely obstructed (5.3%). Although a normal CXR can be identified in CB cases (53.2%), 97.4% of the soldiers had normal CXR imaging in the King study.

TABLE 16-1

CLINICAL FEATURES OF REPORTS OF CONSTRICTIVE BRONCHIOLITIS

Author	N	Smoking History	Etiology	Spirometry	Reduced DLCO	Normal CXR	Normal HRCT	Open Lung Biopsy
Turton et al, 1981 Breatnach and Kerr, 1982	13	0/13	RA-6 Cryptogenic-7	Obst-10/10	5/10	4/13	NR	0/10
Kraft et al, 1993	4	0/4	Idiopathic	Obst-3/4 Norm-1/4	3/4	1/4	1/3	4/4
Padley et al, 1993	18	NR	Various	Obst-16/16	NR	NR	0/18	2/18
Lai et al, 1996	23	0/23	<i>Sauropus</i> leaves	Obst-23/23	6/17	23/23	0/23	4/23
Yang et al, 1997	24	NR	<i>Sauropus</i> leaves	Obst-24/24	21/24	NR	0/24	4/24
Markopoulou et al, 2002	19	9/19	Various	Obst-11/17 Rest-1/17 Mixed-1/17 Norm-4/17	3/19	NR	0/10	19/19
Akpinar-Elci et al, 2004	9	6/9	Diacetyl	Obst-9/9	2/7	5/9	0/8	1/3
Van Rooy et al, 2007	3	1/3	Diacetyl	Obst-3/3	1/3	NR	0/3	1/3
Parambil et al, 2008	29	4/9	Various	Obst-25/28 Rest-3/28 Norm-1/28	1/1	8/28	0/29	5/29
Ghanei et al, 2007	5	0/5	Mustard gas	Norm-5/5	NR	NR	0/5	5/5
King et al, 2011	38	13/38 (34.2%)	Sulfur 74%	Obst-2/38 (5.3%) Rest-2/38 (5.3%) Mixed-1/38 (2.6%) Norm-33/38 (87%)	23/38 (60.5%)	37/38 (97.4%)	31/38 (81.6%)	38/38 (100%)
TOTAL	147	20/85 (23.5%)	—	Obst-124/139 (89.2%) Norm-11 (7.9%) Rest-4 (2.9%) Mixed-1 (0.7%)	42/85 (49.4%)	41/77 (53.2%)	1/123 (0.8%)	45/128 (35.2%)

CXR: chest X-ray radiography; DLCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; Norm: normal; NR: not reported; Obst: obstructive; RA: rheumatoid arthritis; Rest: restrictive

Data sources: Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J*. 2004;24:298–302. Breatnach R, Kerr I. The radiology of cryptogenic obliterative bronchiolitis. *Clin Radiol*. 1982;33:657–661. Ghanei M, Tazelaar HD, Harandi AA, Peyman M, Akbari HMH, Aslani J. Clinical differentiation between resistant asthma and chronic bronchiolitis: testing a practical approach. *Iran J Allergy Asthma Immunol*. 2007;6:207–214. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med*. 2011;365:222–230. Kraft M, Mortenson RL, Colby TV, Newman L, Waldron JA Jr, King TE Jr. Cryptogenic constrictive bronchiolitis, a clinicopathologic study. *Am Rev Respir Dis*. 1993;148(4 Pt 1):1093–1101. Lai R-S, Chiang AA, Wu M-T, et al. Outbreak of bronchiolitis obliterans associated with consumption of *Sauropus androgynus* in Taiwan. *Lancet*. 1996;348:83–85. Markopoulou KD, Cool CD, Elliot TL, et al. Obliterative bronchiolitis: varying presentations and clinicopathological correlation. *Eur Respir J*. 2002;19:20–30. Padley SP, Adler BD, Hansell DM, Muller NL. Bronchiolitis obliterans: high resolution CT findings and correlation with pulmonary function tests. *Clin Radiol*. 1993;47:236–240. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. *Respirology*. 2008;14:443–448. Turton CW, Williams G, Green M. Cryptogenic obliterative bronchiolitis in adults. *Thorax*. 1981;36:805–810. van Rooy FGBG, Rooyackers JM, Prokop M, Houba R, Smit LAM, Heederik DJJ. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med*. 2007;176:498–504. Yang CF, Wu MT, Chiang AA, et al. Correlation of high-resolution CT and pulmonary function in bronchiolitis obliterans: a study based on 24 patients associated with consumption of *Sauropus androgynus*. *AJR Am J Roentgenol*. 1997;168:1045–1050.

The greatest difference demonstrated is the lack of HRCT findings. While <1% of patients from the combined CB series had a normal HRCT, 81.6% of the biopsied soldiers had normal HRCT findings without evidence of the reported abnormalities typically found in CB (ie, diffuse air trapping, nodular pattern, or mosaicism). Finally, in the combined group of CB cases, surgical lung biopsy was only considered necessary to verify the diagnosis in 35.2% of patients. In the majority of cases, the diagnosis of CB was made based on the clinical presentation, the basis of known exposure, significant nonreversible obstruction, and typical findings on HRCT imaging.

Indications for Surgical Lung Biopsy

A controversial issue from the 2011 King et al³ case series was the routine use of surgical lung biopsy in the evaluation of soldiers with postdeployment dyspnea. Although the soldiers reported a decline in exercise tolerance, the amount of decline did not correlate with objective measures of reduced lung function, such as PFT or imaging findings. Although the DLCO was mildly reduced in 50% of the study cohort, none of the soldiers had diffuse parenchymal changes on CT imaging. Mild air trapping may be identified in normal subjects and is a nonspecific finding on CT imaging.³⁵ Pulmonologists have not advocated a surgical approach in patients with unexplained dyspnea in the absence of CT findings suggestive of parenchymal changes or solely with minimal abnormalities in lung function. There are potential risks with surgical lung biopsy to include general anesthesia, bleeding, infection, chronic thoracic pain, and persistent pneumothorax.³⁶

Numerous studies on the utility of surgical lung biopsy in the diagnosis of ILD have been published. Aside from lung transplant patients, CB has been only infrequently reported.^{37–40} As noted previously, most patients with CB have both of the abnormal imaging features associated with physiological impairment.^{31,32} HRCT has been increasingly included in the investigation of unknown lung disease, particularly when ILD is suspected. Compared with lung parenchymal resolution gained from the CXR and routine CT scan images, HRCT has the ability to identify the features of the lung interstitium. HRCT is most helpful in recognizing ILD and, in certain cases, HRCT may provide a definitive diagnosis. In a study comparing HRCT and pathology in 58 ILD patients, the correct diagnosis was reached by the radiologist in 64% of cases.³⁹ Alternatively, if a surgical procedure is needed, HRCT helps identify the most appropriate site for a lung biopsy.

Characteristic HRCT findings in patients with idiopathic pulmonary fibrosis (IPF) may obviate the need for lung biopsy in certain patients.⁴¹ Orens et al⁴² assessed the sensitivity of HRCT in diagnosing IPF and in determining the degree

of physiological abnormalities in those with IPF, but with a negative HRCT. Of the 25 patients with biopsy-proven IPF, three patients (12%) had a normal HRCT result. Based on composite scoring, their disease was less severe, but they still had moderate reduction in spirometry and lung volumes with a normal DLCO. Physiological testing was determined to be more sensitive than HRCT in detecting mild disease in this patient cohort.

The American Thoracic Society and the British Thoracic Society have published guidelines on the role of transbronchial lung biopsy (TBLB) and BAL in the evaluation of clinically suspected ILD. The American Thoracic Society guideline reports that

- the BAL cellular analysis may be a useful adjunct in patients who lack a typical usual interstitial pneumonia pattern on HRCT;
- an inflammatory cellular pattern may narrow the differential diagnosis, although patterns are non-specific; and
- BAL cellular analysis is insufficient to establish a specific diagnosis.⁴³

The British Thoracic Society guidelines on BAL and TBLB make similar statements (with the exception of suspected IPF) and emphasize the timing of the procedure before initiation of treatment, the usefulness of the procedure in identifying suspected infection or malignancy, and the recognition that TBLB is the initial procedure of choice in those patients likely to have ILD in which small samples may be diagnostic, particularly if the disease has a tendency for bronchocentric involvement.⁴³ There is little question, however, that TBLB has a lower diagnostic yield than does open lung biopsy (59% vs 94%) in the investigation of the etiology of ILD. This procedure may not be indicated in particular cases where diagnostic accuracy is needed for specific treatment options.⁴⁴

No published data exist on the pathological findings in patients with dyspnea who have undergone surgical lung biopsy in the absence of PFT or imaging abnormalities. Three large studies have been conducted on patients with unexplained dyspnea. In these reports, the use of lung biopsy is very limited. The first study by Pratter et al⁴⁵ reviewed the utility of diagnostic studies in 85 patients (mean age: 52 years) with chronic dyspnea (2.9 years). The variety of diagnosed disorders included asthma (29%), ILD (14%), chronic obstructive pulmonary disease (14%), cardiomyopathy (10%), upper airway causes (8%), and numerous other etiologies (25%). Most patients underwent bronchoprovocation testing, and only two had a surgical lung biopsy. A subsequent study by DePaso et al⁴⁶ evaluated 72 patients with chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry. Pulmonary disease was identified in 36%, with the majority having asthma and only two

having ILD. The most common causes were cardiac disease (19%), hyperventilation (14%), and “unexplained” (19%). The most recent study, specifically performed on 105 military personnel with exertional dyspnea, demonstrated a different spectrum of disease.³³ This study had a corresponding control group ($n = 69$), and all patients underwent a standardized evaluation. Airways obstruction (exercise-induced bronchospasm, asthma, bronchitis, and emphysema) was by far the most frequent explanation for dyspnea (52%). Of the remainder, 10% had vocal cord dysfunction, 14% had other disorders, and 24% had no discernible etiology despite comprehensive testing. With the exception of two patients diagnosed with sarcoidosis, lung biopsy (bronchoscopic or surgical) was not indicated.

A recent study published by Doyle et al⁴⁷ provides a

reasonable perspective on the proposed evaluation for subclinical lung disease. They evaluated smokers and patients at risk for developing pulmonary fibrosis (to include familial pulmonary fibrosis) and rheumatoid arthritis. In these patients with clinically suspected ILD or others with incidentally noted interstitial lung abnormalities found on HRCT, the risk for progression is unclear. Their algorithm outlined the evaluation process and suggested that, in the absence of symptoms or physiological impairment on full PFTs, patients can be followed periodically for progression of HRCT findings, symptoms, or physiological changes on PFTs prior to a formal ILD evaluation. The authors emphasized that a primary step after a nondiagnostic HRCT is the utilization of BAL cellular analysis to narrow the differential diagnosis before proceeding with surgical lung biopsy.

EVALUATION OF WORLD TRADE CENTER RESPONDERS

The evaluation of firefighters, police, and other persons exposed to the airborne hazards associated with the 2001 WTC collapse is an excellent example of repeated inhalation exposures of particulate matter exposure in a defined population. Numerous studies have been published as part of the systematic evaluation of respiratory complaints made after exposure to the WTC dusts. A spectrum of pulmonary diseases has been diagnosed that reflects chronic inflammation of the lung with associated airflow obstruction. These diseases include irritant-induced asthma, chronic bronchitis, aggravated preexisting asthma or chronic obstructive pulmonary disease, and bronchiolitis. To a lesser extent, chronic rhinosinusitis, upper airway disease, and gastroesophageal reflux were noted in this population, with uncommon reports of ILD (eg, sarcoidosis or interstitial pulmonary fibrosis).⁴⁸ Evaluation of WTC dust demonstrated predominantly coarse particles (955) with high alkalinity (pH of 9.0–11.0). The high alkalinity of this dust produced bronchial hyperreactivity, persistent cough, and increased risk of asthma.⁴⁹

Increased symptoms were commonly reported in heavily exposed areas. New-onset respiratory symptoms were described by 55.8% of area residents (survey of 2,812 persons) in an exposed area, compared with 20.1% in the control area. Persistent symptoms were identified in 26.4% of residents in the exposed area versus 7.5% in the control areas, but no differences in screening spirometry were detected.⁵⁰

Examinations of 9,442 responders from 2002 to 2004 identified 69% who experienced new or worsened respiratory symptoms while performing work at the WTC site.⁵¹ Pulmonary function analysis of symptomatic individuals was notable for a variety of findings. Results from the WTC Worker and Volunteer Medical Screening Program identified 61% with new-onset respiratory symptoms that persisted after the WTC attacks. Twenty-eight percent of all tested individuals had abnormal spirometry; FVC was below the 95th

percentile in 21%, and obstruction was present in 5%. The rate of abnormal spirometry was 27% among nonsmokers (compared with 13% in the general US population), and the prevalence of low FVC among nonsmokers (20%) was five-fold greater than the US population. Respiratory symptoms and spirometry abnormalities were significantly associated with early arrival at the WTC site.

Longitudinal studies showed a reduction in adjusted average FEV₁ in WTC-exposed workers for the year following exposure, and the decrement correlated with intensity of exposure and the presence of respiratory symptoms.⁵² Spirometry in nearly 13,000 fire department workers showed a reduction in FEV₁ (affecting 13% of firefighters and 22% of the emergency medical services personnel), with little recovery over the 6-year follow-up period.⁵³ In an early study of 179 workers, hyperreactivity was increased 6.8 times for those highly exposed, compared with those moderately exposed, and it persisted beyond 6 months in 55% of workers with airway hyperreactivity.⁵⁴

Evidence for other lung diseases is relatively uncommon despite the extensive follow-up care these patients received. Pathological evidence consistent with new-onset sarcoidosis was found in 26 patients. Thirteen patients were identified during the first year after the initial WTC disaster, and the remaining 13 patients were identified over the next 4 years. In this cohort, a high percentage (69%) had airway hyperreactivity not previously seen in sarcoidosis patients from this area.⁵⁵ There is a single case report of a patient with granulomatous pneumonitis who developed cough and dyspnea 3 weeks postexposure with diffuse miliary nodularity on imaging and lung biopsy showing diffuse, noncaseating granulomatous nodules and large quantities of silicates by electron microscopy.⁵⁶ A single case of acute eosinophilic pneumonia was reported in a firefighter with 70% eosinophilia on BAL.⁵⁷ Only one

patient was reported to have CB identified by surgical lung biopsy. Despite the lack of radiographic findings and a normal HRCT, he demonstrated chronic unresponsive respiratory symptoms and a 50% reduction in FVC.²¹ In this case, the patient's progressive respiratory decline was unresponsive to corticosteroid therapy, but did improve following chronic azithromycin therapy.⁵⁸

Overall, surgical lung biopsy in this large symptomatic population was a relatively rare procedure for interstitial changes or unexplained pulmonary disease. Wu et al⁵⁹ reported on seven WTC responders with severe respiratory impairment or unexplained radiological findings. Histopa-

thology showed ILD consistent with small airways disease, bronchiolocentric parenchymal disease, and nonnecrotizing granulomas. Tissue analysis for minerals showed variable amounts of substances, including silicates, asbestos, calcium compounds, shards of glass, and carbon nanotubes.⁵⁹ Similar findings were noted in a study of 12 patients who underwent surgical lung biopsy for suspected ILD or abnormal PFTs (predominantly restrictive with normal imaging).⁶⁰ Findings included interstitial fibrosis, emphysematous change, and small airway abnormalities. All cases had particles within macrophages containing silica, aluminum silicates, titanium dioxide, talc, and metals.

SUMMARY

The clinical approach to the deployed military patient with unexplained respiratory complaints should be comprehensive. Based on limited data, the association between deployment in Iraq or Afghanistan and the development of chronic lung disease is not well defined at this time. Patients with postdeployment respiratory symptoms should receive a comprehensive, noninvasive evaluation that includes a detailed history of inhalational exposures, examination, complete PFTs, CXR, HRCT, and routine testing to eliminate asthma as the causative etiology. Bronchoscopy with BAL and TBLB (if indicated) may provide additional information for evidence of inflammatory or infectious etiologies. For most

deployed military personnel with unexplained dyspnea, close observation with interval imaging and PFTs can determine any progressive nature to their underlying symptoms. Invasive testing, such as surgical lung biopsy, should be reserved for only those patients with significant PFT or imaging abnormalities who have shown no improvement over time. As noted by Ryu⁶¹ in his 2006 review of bronchiolar disease, the finding of "bronchiolitis" on lung biopsy may either be a major finding or a minor component of the underlying disorder and not relevant to the final diagnosis. The clinician must determine the relevance of this finding with clinical, radiological, and physiological findings.

REFERENCES

1. Weese CB, Abraham JH. Potential health implications associated with particulate matter exposure in deployed settings in southwest Asia. *Inhal Toxicol*. 2009;21:291–296.
2. Institute of Medicine of the National Academies. *Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan*. Washington, DC: The National Academies Press; 2011: 1–9, 31–44, 117–129.
3. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med*. 2011;365:222–230.
4. Smith B, Wong CA, Smith TC, Boyko EJ, Gackstetter G, Ryan MAK. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: a prospective population-based study. *Am J Epidemiol*. 2009;170:1433–1442.
5. Abraham JH, DeBakey SF, Reid L, Zhou J, Baird CP. Does deployment to Iraq and Afghanistan affect respiratory health of US military personnel? *J Occup Environ Med*. 2012;54:740–745.
6. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among US military personnel deployed in or near Iraq. *JAMA*. 2004;292:2997–3005.
7. Sine C, Allan P, Haynes R, et al. Case series of 44 patients with idiopathic acute eosinophilic pneumonia in the deployed military setting [abstract]. *Chest*. 2011;140:675A.
8. Roop SA, Niven AS, Calvin BE, Bader J, Zacher LL. The prevalence and impact of respiratory symptoms in asthmatics and non-asthmatics during deployment. *Mil Med*. 2007;172:1264–1269.

9. Szema AM, Peters MC, Weissinger KM, Gagliano CA, Chen JJ. New-onset asthma among soldiers serving in Iraq and Afghanistan. *Allergy Asthma Proc.* 2010;31:67–71.
10. Delvecchio, S, Zacher L, Morris M. Correlation of asthma with deployment in active duty military personnel [abstract]. *Chest.* 2010;138:145A.
11. Rawlins F, Morris M. Pulmonary evaluation of active duty military personnel for deployment-related respiratory symptoms [abstract]. *Chest.* 2012;142:749A.
12. Epler GR. Constrictive bronchiolitis obliterans: the fibrotic airway disorder. *Expert Rev Respir Med.* 2007;1:139–147.
13. Kraft M, Mortenson RL, Colby TV, Newman L, Waldron JA Jr, King TE Jr. Cryptogenic constrictive bronchiolitis, a clinicopathologic study. *Am Rev Respir Dis.* 1993;148(4 Pt 1):1093–1101.
14. King TE Jr. Miscellaneous causes of bronchiolitis: inhalational, infectious, drug-induced, and idiopathic. *Semin Respir Crit Care Med.* 2003;24:567–576.
15. Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med.* 2002;347:330–338.
16. Akpınar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J.* 2004;24:298–302.
17. Ghanei M, Harandi AA. Long term consequences from exposure to sulfur mustard: a review. *Inhal Toxicol.* 2007;19:451–456.
18. Ghanei M, Tazelaar HD, Chilosi M, et al. An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. *Respir Med.* 2008;102:825–830.
19. Ghanei M, Tazelaar HD, Harandi AA, Peyman M, Akbari HMH, Aslani J. Clinical differentiation between resistant asthma and chronic bronchiolitis: testing a practical approach. *Iran J Allergy Asthma Immunol.* 2007;6:207–214.
20. Mann JM, Sha KK, Kline G, Breuer FU, Miller A. World Trade Center dyspnea: bronchiolitis obliterans with functional improvement: a case report. *Am J Ind Med.* 2005;48:225–229.
21. Lai R-S, Chiang AA, Wu M-T, et al. Outbreak of bronchiolitis obliterans associated with consumption of *Sauropus androgynus* in Taiwan. *Lancet.* 1996;348:83–85.
22. Yang CF, Wu MT, Chiang AA, et al. Correlation of high-resolution CT and pulmonary function in bronchiolitis obliterans: a study based on 24 patients associated with consumption of *Sauropus androgynus*. *AJR Am J Roentgenol.* 1997;168:1045–1050.
23. Garg K, Lynch DA, Newell JD, King TE Jr. Proliferative and constrictive bronchiolitis: classification and radiologic features. *AJR Am J Roentgenol.* 1994;162:803–808.
24. de Jong PA, Dodd JD, Coxson, HO, et al. Bronchiolitis obliterans following lung transplantation: early detection using computed tomographic scanning. *Thorax.* 2006;61:799–804.
25. Breatnach R, Kerr I. The radiology of cryptogenic obliterative bronchiolitis. *Clin Radiol.* 1982;33:657–661.
26. Padley SP, Adler BD, Hansell DM, Muller NL. Bronchiolitis obliterans: high resolution CT findings and correlation with pulmonary function tests. *Clin Radiol.* 1993;47:236–240.
27. Leung AN, Fisher K, Valentine V, et al. Bronchiolitis obliterans after lung transplantation: detection using expiratory HRCT. *Chest.* 1998;113:365–370.
28. Worthy SA, Park CS, Kim JS, Muller NL. Bronchiolitis obliterans after lung transplantation: high resolution CT findings in 15 patients. *AJR Am J Roentgenol.* 1997;169:673–677.

29. Lee ES, Gotway MB, Reddy GP, Golden JA, Keith FM, Webb WR. Early bronchiolitis obliterans following lung transplantation: accuracy of expiratory thin-section CT for diagnosis. *Radiology*. 2000;216:472–477.
30. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. *Respirology*. 2008;14:443–448.
31. Markopoulou KD, Cool CD, Elliot TL, et al. Obliterative bronchiolitis: varying presentations and clinicopathological correlation. *Eur Respir J*. 2002;19:20–30.
32. van Rooy FGBG, Rooyackers JM, Prokop M, Houba R, Smit LAM, Heederik DJJ. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med*. 2007;176:498–504.
33. Baird CP, DeBaakey S, Reid L, Hauschild VD, Petruccielli B, Abraham JH. Respiratory health status of US Army personnel potentially exposed to smoke from 2003 Al-Mishraq Sulfur Plant fire. *J Occup Environ Med*. 2012;54:717–723.
34. Turton CW, Williams G, Green M. Cryptogenic obliterative bronchiolitis in adults. *Thorax*. 1981;36:805–810.
35. Tanaka N, Matsumoto T, Miura G, et al. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. *Radiology*. 2003;227:776–785.
36. Zhang D, Liu Y. Surgical lung biopsies in 418 patients with suspected interstitial lung disease in China. *Intern Med*. 2010;49:1097–1102.
37. Sigurdsson MI, Isaksson HJ, Gudmundsson G, Gudbjartsson T. Diagnostic surgical lung biopsies for suspected interstitial lung diseases: a retrospective study. *Ann Thorac Surg*. 2009;88:227–232.
38. Ayed AK. Video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse interstitial lung disease. A prospective study. *J Cardiovasc Surg*. 2003;44:115–118.
39. Fibla JJ, Molins L, Blanco A, et al. Video-assisted thoracoscopic lung biopsy in the diagnosis of interstitial lung disease: a prospective, multi-center study in 224 patients. *Arch Bronconeumol*. 2012;48:81–85.
40. Swensen SJ, Aughenbaugh GL, Myers JL. Diffuse lung disease: diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. *Radiology*. 1997;205:229–234.
41. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*. 2012;185:1004–1014.
42. Orens JB, Kazerooni EA, Martinez FJ, et al. The sensitivity of high-resolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy. A prospective study. *Chest*. 1995;108:109–115.
43. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*. 2008;63(suppl 5):v1–v58.
44. Rizzato G. The role of thoracic surgery in diagnosing interstitial lung disease. *Curr Opin Pulm Med*. 1999;5:284–286.
45. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. *Arch Intern Med*. 1989;149:2277–2282.
46. DePaso WJ, Winterbauer RH, Lusk JA, Dreis DF, Springmeyer SC. Chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry. Analysis of a seven-year experience. *Chest*. 1991;100:1293–1299.
47. Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: why you should care. *Am J Respir Crit Care Med*. 2012;185:1147–1153.
48. Guidotti TL, Prezant D, de la Hoz RE, Miller A. The evolving spectrum of pulmonary disease in responders to the World Trade Center tragedy. *Am J Ind Med*. 2011;54:649–660.

49. Landrigan PJ, Lloy PJ, Thurston G, et al. Health and environmental consequence of the World Trade Center disaster. *Environ Health Perspect.* 2004;112:731–739.
50. Reibman J, Lin S, Hwang SA, et al. The World Trade Center residents' respiratory health study: new-onset respiratory symptoms and pulmonary function. *Environ Health Perspect.* 2005;113:406–411.
51. Herbert R, Moline J, Skloot G, et al. The World Trade Center disaster and the health of workers: five-year assessment of a unique medical screening program. *Environ Health Perspect.* 2006;114:1853–1858.
52. Banauch GI, Hall C, Weiden M, et al. Pulmonary function after exposure to the World Trade Center collapse in the New York City Fire Department. *Am J Respir Crit Care Med.* 2006;174:312–319.
53. Aldrich TK, Gustave J, Hall CB, et al. Lung function in rescue workers at the World Trade Center after 7 years. *N Engl J Med.* 2010;362:1263–1272.
54. Banauch GI, Alleyne D, Sanchez R, et al. Persistent hyperreactivity and reactive airway dysfunction at the World Trade Center. *Am J Respir Crit Care Med.* 2003;168:54–62.
55. Izbicki G, Chavko R, Banauch GI, et al. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest.* 2007;13:1414–1423.
56. Safirstein BH, Klukowicz A, Miller R, Teirstein A. Granulomatous pneumonitis following exposure to World Trade Center collapse. *Chest.* 2003;123:301–304.
57. Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med.* 2002;166:797–800.
58. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med.* 2003;168:121–125.
59. Wu M, Gordon RE, Herbert R, et al. Case report: lung disease in World Trade Center responders exposed to dust and smoke: carbon nanotubes found in the lungs of World Trade Center patients and dust samples. *Environ Health Perspect.* 2010;118:499–504.
60. Caplan-Shaw CE, Yee H, Rogers L, et al. Lung pathologic findings in a local residential and working community exposed to World Trade Center dust, gas, and fumes. *J Occup Environ Med.* 2011;53:981–991.
61. Ryu JH. Classification and approach to bronchiolar diseases. *Curr Opin Pulm Med.* 2006;12:145–151.